

The Lost Art of Whole Blood Transfusion in Austere Environments

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Abstract

The optimal resuscitation fluid for uncontrolled bleeding and hemorrhagic shock in both pre- and in-hospital settings has been an ongoing controversy for decades. Hemorrhage continues to be a major cause of death in both the civilian and military trauma population, and survival depends on adequacy of hemorrhage control and resuscitation between onset of bleeding and arrival at a medical treatment facility. The terms far-forward and austere are defined, respectively, as the environment where professional health care providers normally do not operate and a setting in which basic equipment and capabilities necessary for resuscitation are often not available. The relative austerity of a treatment setting may be a function of timing rather than just location, as life-saving interventions must be performed quickly before hemorrhagic shock becomes irreversible. Fresh whole blood transfusions in the field may be a feasible life-saving procedure when facing significant hemorrhage.

significant melena. The combination of high altitude and bad weather prevented helicopter evacuation. During the 3-h walk to base camp, the author experienced loss of color vision, poor acuity, and severely impaired balance. He fell several times on descent, luckily without further injuries. On arrival at the base camp medical station, the patient was exhausted, barely able to walk, and had tachycardia and hypotension. The medics on site were unable to obtain a vascular access, which presented yet another significant challenge.

Introduction

Aconcagua Emergency

In January 2005 on the Andes mountain range, a group of Norwegian climbers attempted summiting Aconcagua from the east side. Situated on the False Polish Glacier route approximately 5,000 m above sea level, one of the authors experienced muscle soreness and stiffness because of strenuous exercise and a heavy backpack during climbing. He decided to self-medicate on the afternoon before summiting. A few hours after ingesting 1,000 mg of paracetamol and 20 mg of piroxicam, he experienced moderate hallucinations and shortness of breath. That morning, he briefly lost consciousness three times during morning routines and had

The optimal resuscitation fluid for uncontrolled bleeding and hemorrhagic shock both in pre- and in-hospital settings has been an ongoing controversy for decades (4). Hemorrhage continues to be a major cause of death in both the civilian and military trauma population, and survival depends on adequacy of hemorrhage control and resuscitation between onset of bleeding and arrival at a medical treatment facility. The terms far-forward and austere are defined respectively as the environment where professional health care providers normally do not operate and a setting in which basic equipment and capabilities necessary for resuscitation are often not available (10). The relative austerity of a treatment setting may be a function of timing rather than just location, as life-saving interventions must be performed quickly and before hemorrhagic shock becomes irreversible.

Military medical advisors acknowledge that far-forward resuscitation remains one of the great challenges of combat casualty care and that there is a need to improve field management of traumatic bleeding. Civilian injury patterns are often not comparable with the wound profiles encountered on the battlefield, but ultimately some combination of tissue damage and duration of hemorrhage results in the physiology of oxygen debt and the presence of acute traumatic coagulopathy (ATC). The timing and degree to which oxygen debt is repaid while mitigating ATC are the

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keys to survival and avoidance of organ failure. This leaves us with the unanswered question: what is the best treatment for the bleeding hiker or wounded soldier?

So what is the major problem of hemorrhage when evacuation is delayed? It is well-known that a bleeding patient faces a steadily increased risk of death due to oxygen debt accumulation, causing acidosis, coagulopathy, and hypothermia. The latter combination commonly is called the “lethal triad” (6,12).

The Remote Damage Control Resuscitation (RDCR) meetings, held annually in Norway since 2011 and sponsored by the Norwegian Naval Special Operations Command, the Norwegian Air Ambulance, and the Trauma and Hemostasis Oxygenation and Resuscitation Network, has gathered leaders in far-forward resuscitation to find the optimum strategy that addresses both oxygen debt and coagulopathy.

The goal always will be to obtain early hemorrhage control. In the event of delayed intervention, a permissive strategy with low-volume resuscitation keeping systolic blood pressure (BP) between 80 and 90 mm Hg has gained worldwide acceptance and has been shown to improve outcomes. It must be stressed that this approach only has been validated in patients receiving crystalloid resuscitation and facing short evacuation times (3,7). It is unlikely to be safe or efficacious with significantly delayed evacuation and definitive treatment unless blood products are included in resuscitation.

After decades with a crystalloid- or colloid-based hemorrhagic shock resuscitation in the prehospital setting and a red cell component-based strategy in-hospital, the current guidelines now point to replacement of blood loss with blood components as soon as feasible (4). Although there is no universal agreement on red cell:plasma:platelet ratios, the damage control resuscitation (DCR) strategy uses a 1:1:1 mix of components (practically, which translates into 6 red blood cells (RBC) units, 6 fresh frozen plasma (FFP) units, and 1 apheresis platelet unit) (8).

The key aspects of DCR include the following: permissive hypotension, prevention or treatment of hypothermia, acidosis and hypocalcemia, avoidance of hemodilution by minimizing use of clear fluids, early transfusion of blood products delivering whole blood functionality (components or whole blood), and rapid definitive surgical control of bleeding (3,27). In addition, there is strong evidence that early administration of the antifibrinolytic, tranexamic acid (TXA) reduces mortality. The mechanism is probably by inhibiting fibrinolysis and thus improving clot strength and reducing the impact of ATC (20). In major blood loss, fibrinogen is a key factor in clot strength and it is consumed rapidly during massive hemorrhage. Maintaining a normal fibrinogen concentration seems to be a reasonable approach, although this has not been validated in randomized trials. There is growing evidence that a standardized strategy with early coagulation monitoring using thromboelastography (TEG/ROTEM) and goal-directed therapy improves outcomes (11,25).

All agree that the goal of DCR is to offer the patient optimal care as early as possible, but there are major challenges in implementing these strategies when facing delayed evacuation in an austere environment.

Emergency Medical Services (EMS) systems, expedition medicine, and military combat casualty care largely have based their resuscitation strategy on permissive hypotension with crystalloid and colloid therapy, followed by prevention of hypothermia and early administration of TXA. Sadly, history has shown that hemorrhagic shock resuscitation with crystalloids and colloids is insufficient — described by Gordon Watson as early as 1918 as follows: “There was no comparison between the results of transfusion, which were instantaneous and permanent, and those secured by infusions of saline, which were ‘a flash in the pan’ and followed by more serious collapse” (21). Even though history and recent research and experience have shown that this strategy is sub-optimal, one may wonder — is there any other better option?

Because of the nature of the austere environment, several factors have to be addressed; weight and bulkiness especially can be of great importance. Medics working in high altitudes know that even carrying a single bag of saline greatly contributes to physical effort. Shifting climate conditions make it nearly impossible to store blood components in a proper manner.

Hypotensive Resuscitation Preserves Coagulation and Reduces Bleeding while Sacrificing Perfusion — How Do We Preserve Maximum Delivery of Oxygen in the “Low-Flow State”?

Delivery of oxygen (DO_2) to the tissues is calculated as the oxygen binding capacity of hemoglobin \times the concentration of hemoglobin \times the saturation of hemoglobin + the amount of dissolved oxygen in blood all multiplied by the cardiac output (CO), called the Fick equation: $\text{DO}_2 = [1.31 \times \text{Hb} \times \text{SaO}_2 + (0.003 \times \text{PaO}_2)] \times \text{CO}$.

It explains the relationship between the three different factors responsible for oxygen delivery. CO cannot be inferred from BP in patients with ongoing bleeding (28). The poor correlation between CO and BP in the bleeding patient still remains a challenge, and simple noninvasive monitoring devices with the capability of identifying “early reduced perfusion” are lacking. The explanation on why CO correlates poorly with BP is found in the Ohm’s law of systemic circulation, as follows: $\text{BP} = \text{CO} \times \text{systemic vascular resistance (SVR)}$.

Increasing sympathetic tone will increase SVR when CO is decreasing, keeping BP within an acceptable range.

Not until SVR has reached its maximum will a further reduction in CO cause a significant drop in BP. A strong correlation between CO and BP in healthy individuals does not appear until half of the blood volume is lost or unless bleeding occurs very rapidly.

Hypotensive (permissive) resuscitation is used to describe a resuscitation approach that minimizes administration of fluids until hemorrhage control has been achieved. Small volumes given intravenously or intraosseously will increase the CO and hence the BP because the circulation is constricted severely with low circulating blood volume.

Nevertheless, hypotensive resuscitation sacrifices perfusion to preserve coagulation and reduce the ongoing bleeding.

The Fick equation shows that the most sustainable method of keeping DO_2 at the highest possible level while CO remains low is to transfuse something that keeps the patient’s hemoglobin concentration close to normal.

During prolonged hypotensive resuscitation, hemodilution with clear fluids will decrease steadily the hemoglobin while keeping the CO relatively constant (systolic BP, 80 to 90 mm Hg). This process results in a steady decline in DO_2 .

A mixture of red cells:plasma:platelets in a 1:1:1 ratio contains a hemoglobin concentration of around $9 \text{ g}\cdot\text{dL}^{-1}$ due to the anticoagulants and red cell additive solutions. Whole blood (approximately 450 mL of blood + 63 mL of preservation solution) has an average hematocrit of 40% to 45%, which gives an average hemoglobin level of 13 to $14 \text{ g}\cdot\text{dL}^{-1}$. According to the Fick equation, the whole blood approach gives a DO_2 30% higher than the component approach in a replacement transfusion.

Hemostasis and “Blood Failure”

Optimal resuscitation of hemorrhagic shock should address both oxygen delivery and hemostasis (4,18). Ongoing noncompressible bleeding causes loss of platelets in different ways. They are lost because they leave the circulation at the bleeding site(s) and are consumed as the body tries to stop the bleeding by making clots. Furthermore, platelet dysfunction is observed in combination with severe trauma or drugs that cause platelet inhibition (13). Plasma is lost while leaving the circulation at the bleeding site(s), and coagulation factors and inhibitors in plasma are consumed in the clotting process, often combined with activation of anticoagulating enzymes. Oxygen delivery is compromised by loss of red cell mass and reduced CO. The previously mentioned is a simplified explanation of how the three most important parts of the blood (platelets, plasma, and red cells) fail because of severe bleeding and why this might be called “blood failure.” A sensible approach to life-threatening organ failure is to replace it with a functional organ. In the austere setting where standard blood components are unavailable, fresh whole blood is a viable option (16).

When red cells are lost, there is evidence that whole blood resuscitation is superior to stored red cell concentrate and plasma transfusion alone (17). The U.S. Committee on Tactical Combat Casualty Care guidelines recommend whole blood as the number one preferred fluid for hemorrhagic shock resuscitation in combat casualties (4).

History of Whole Blood Transfusion — Why Abandoned?

The benefits of whole blood transfusion for hemorrhagic shock became apparent in World War (WW) I. Blood banking and transfusion medicine have since undergone an evolution that has favored component therapy as a means of delivering a maximal range of products to a maximum number of patients. However, group O whole blood was used originally as universal blood. Late during WW II, titrating of anti-A/anti-B antibodies was standardized and what was called low-titer group O was preferred as universal blood to avoid minor ABO incompatibility. From WW I until the Vietnam era, whole blood became the backbone of hemorrhagic shock resuscitation (15). Gradually blood banks replaced whole blood with components without thorough investigation of outcomes in patient populations with massive bleeding. Later the discoveries that blood transfusion could transmit hepatitis B and C and HIV made a great impact on transfusion practices. Increasing costs of transfusion and concerns that storage

under refrigeration would lead to loss of functional platelets led to the abandonment of whole blood transfusion. Recently the concerns regarding whole blood hemostatic function have been shown to be misplaced (19). Currently, fear of transfusion complications, especially transfusion-transmitted diseases (TTD), sometimes seems to overshadow the benefit of fresh whole blood transfusion in settings where no other alternative exists. This represents flawed risk/benefit analysis.

Prehospital mortality from traumatic hemorrhagic shock is approximately 30% to 40%. When considering transfusion risk in the face of major bleeding, one must weigh the risks of TTD and transfusion reactions in relation with the potential benefit of transfusion. In Norway, the seroconversion rate (HIV and hepatitis B and C) is 4.5/100,000 (2012) in regular blood donors. Blood transfused untested implies a risk of TTD of 1:20,000. Rapid testing 5 min before transfusion reduces risk to approximately 1:250,000. The risk of death from exsanguination may range from 30% to 100%. In situations of serious bleeding, the risk/benefit analysis highly favors the use of walking blood donors.

In-the-Field Issues

The prehospital environment is a challenging place to treat shock (9).

When implementing whole blood transfusion protocols, one of the difficult questions is to understand when to initiate and how to evaluate the effect of blood transfusion (9).

Identification of occult shock development is a major clinical problem. Furthermore there are no reliable criteria assessing the efficacy of fluid resuscitation (2). Advanced trauma life support (ATLS) principles advocate volume resuscitation with crystalloids and subsequent blood transfusion resuscitation when there are signs of obvious blood loss and tissue hypoperfusion (1). Clinical parameters include decreased systolic BP ($<90 \text{ mm Hg}$), elevated heart rate ($>120 \text{ bpm}$), and reduced urinary output ($<15 \text{ mL}\cdot\text{h}^{-1}$). Laboratory tests to evaluate signs of anaerobic metabolism due to oxygen debt include lactate, base deficit, and bicarbonate (26). These tests may help evaluate the severity of shock. Other tests include echocardiographic signs of hypovolemia, venous oxygen saturation, and oxygen extraction. Tissue oxygenation monitors (STO_2) also may help in the decision making process (14). Many of these parameters are not available in the prehospital setting, making the decision even more difficult.

As we are waiting for a reliable, lightweight, and robust monitor that says “give blood” or “wait,” we still have to rely on well-known parameters. In a report from Afghanistan, a silver star-recipient physician assistant performed prolonged field care whole blood transfusion over 17 h using mentation as one of the reliable transfusion triggers (5).

It is important to understand the physiology of shock and acknowledge that the timing and degree to which oxygen debt is repaid are the keys to survival and mitigation of organ failure (2).

We suggest reliable parameters of careful evaluation of the mechanism of hemorrhage, mentation, heart rate, and systolic BP. Small lactate monitors can be brought along easily even in the most challenging conditions and can be of importance in evaluating the effect of resuscitation in prolonged care situations. STO_2 monitors also may be

Royal Caribbean Cruises Ltd - Blood Transfusion Protocol for Shipboard Management of Catastrophic, Non-Compressible Hemorrhage

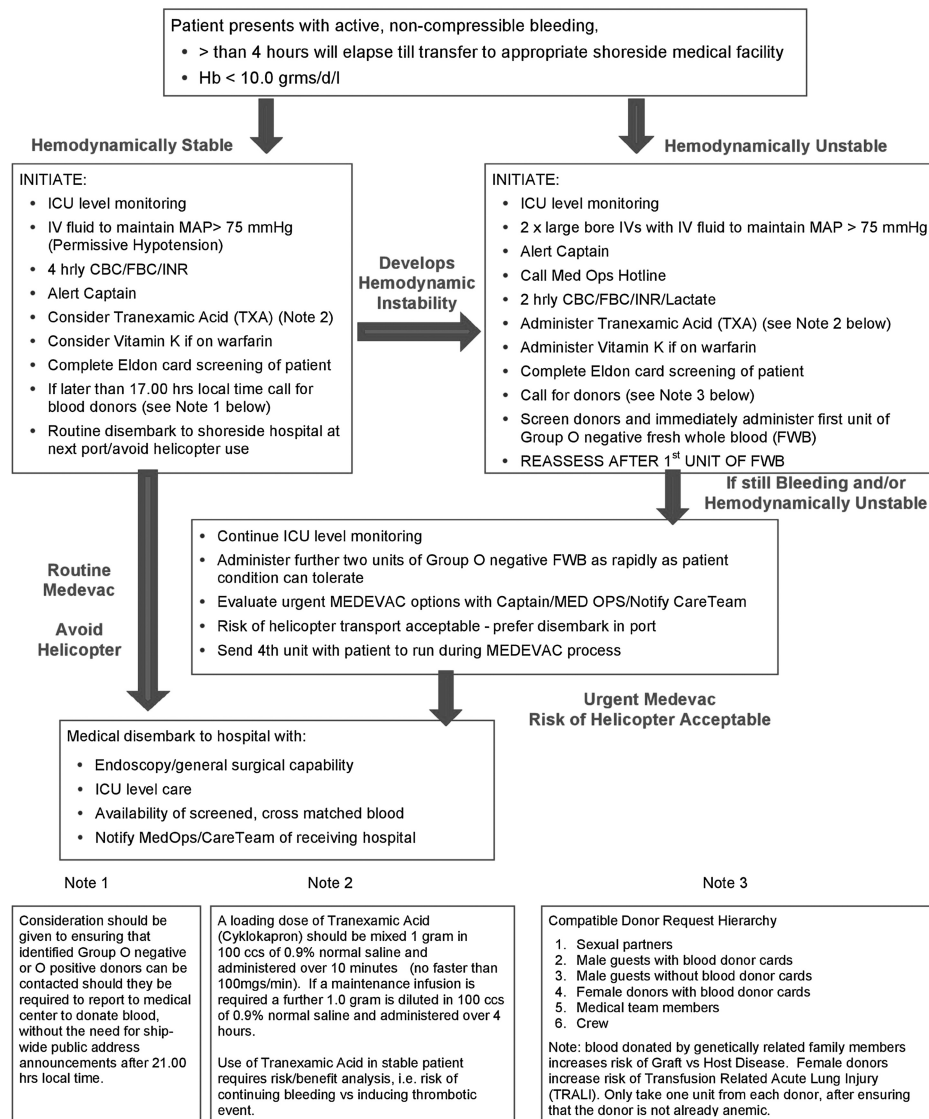


Figure 1: Example of blood transfusion protocol for shipboard management of catastrophic, non-compressible hemorrhage.

helpful in certain conditions, but currently there are no monitors that meet all the standards of prehospital use.

Critics may claim that warm fresh whole blood (WFWB) transfusion protocols in remote locations are hazardous and put the donor at risk. The same questions arose in the Norwegian Naval Special Operations Commando (NORNAVSO) when they evaluated their resuscitation protocols in 2009. Making WFWB available in the far-forward environment became one of their main goals, and postdonation performance had to be evaluated before a protocol could be implemented. Researchers linked to the Naval Special Operation Forces (SOF) community designed and completed two studies examining this subject (24). The parameters of oxygen uptake, shooting skills for cognitive purposes, and mountain hiking were investigated. Results from the first study are published, and they show negligible changes in performance. The initial study was designed so that the subjects performed $\dot{V}O_{2max}$, shooting,

and hiking tests under ideal circumstances, meaning not under any other strain or duress except from the testing itself. Furthermore, they completed a second donor performance study evaluating the effects of phlebotomy, when dehydrated and fatigued, on oxygen uptake. These unpublished data showed a 7% to 11% decrease in maximal oxygen uptake. Both of these studies had an exceptional subject population, limited to Special Forces soldiers, and the first study did not have a control group. The last study that showed a decrease in $\dot{V}O_{2max}$ was a double-blinded study with a control group. Despite these pitfalls, the results adequately convinced and assured the command of the military unit such that they implemented a remote resuscitation protocol with WFWB as an option.

A thoughtful risk/benefit analysis concluded that the risk of compromising one soldier's $\dot{V}O_{2max}$ levels by approximately 10% does not outweigh the benefit for a patient with hemorrhage with a 30% to 40% risk of death. When

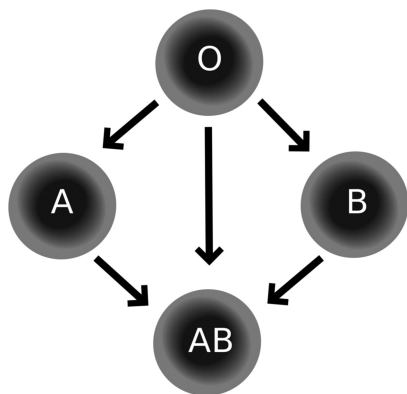


Figure 2: Which group can donate blood to which other type of blood group.

it comes to donor performance in high-altitude situations, further investigations are warranted.

The Austere Maritime Environment — Cruise Ship Transfusions

Royal Caribbean Cruises Ltd. (RCCL) operates 35 cruise ships that by the end of 2014 will have taken 4.9 million guests to visit 300 ports in over 100 countries. With worldwide itineraries in increasingly remote areas of the world, access to rapid patient evacuation and blood products is a huge challenge when managing a patient with acute blood loss. Logistics constraints make stocking blood products on board impractical, and so the 85 physicians and 140 nurses who work on RCCL ships all have been trained to administer WFWB, collected on board the cruise ship, when the patient condition suggests that they will die unless they receive blood.

Since the RCCL blood transfusion program was introduced in 2009, they have provided WFWB to 58 patients, administering between 1 and 6 units of blood to patients facing imminent demise due to blood loss. The vast majority of the clinical cases were blood loss due to gastrointestinal bleeding, often exacerbated by the use of antiplatelet agents or blood thinners taken for underlying cardiovascular conditions. It is just this patient subgroup, patients with cardiovascular disease, in which several studies have demonstrated decreased tolerance of acute blood loss compared with patients without an underlying cardiovascular disease.

The 57 patients who received WFWB presented to the shipboard medical teams with an average initial hemoglobin of 5.96 g/dL^{-1} . When confronted with a patient needing blood products, the shipboard medical team will make an announcement for guests who are blood donors to come to the onboard medical center for review to see whether they are potentially compatible blood donors. Calls for blood donors typically yield between four and eight guests who are frequent blood donors. Their blood group will be determined by testing using the Eldon card system, and then if they are blood group O negative or positive and potential donors, they will then be screened for HIV and hepatitis B and C using rapid tests.

RCCL medical teams are encouraged to obtain informed consent for blood transfusion as soon as it becomes clear that this will be necessary. It is clearly preferable to allow the patient to consider the options while they are relatively alert, rather than wait for them to lapse into hemodynamic instability, and then discuss the issues.

The RCCL WFWB transfusion protocol (Fig. 1) uses onset of hemodynamic instability as the trigger for WFWB transfusion, rather than some arbitrary level of hemoglobin. In addition to the administration of WFWB, consideration is given to the administration of TXA early in the management of the patient with hemorrhage.

Of the 57 patients who have undergone transfusion, 51 survived to hospital discharge home. RCCL's assessment of the patients who have undergone transfusion to date is that of these survivors, more than 40 would have died without transfusion. RCCL staff report that as well as providing clear resuscitation benefit over crystalloid, WFWB provides therapeutic benefit, particularly for those patients on antiplatelet agents and blood thinners, helping promote clotting (Fig. 1).

Practical Approach — How to Prepare the Expedition for a WFWB Backup

As mentioned earlier, weight and bulkiness are a major concern in the out-of-hospital setting. Fluids like the Ringer lactate and saline contribute to the weight of the equipment set. Storage conditions like freezing temperatures on one hand and high temperatures on the other also can complicate storage in the field. We also know that a whole blood-based resuscitation strategy is superior to a crystalloid/colloid approach even when augmented by a limited number of RBC and plasma units. No current evacuation system, military or civilian, is capable of providing blood components like RBC, platelets, and plasma in a prehospital setting and especially in the austere setting.

To overcome these problems, WFWB can be stored and transported under perfect conditions in the body of the donor and then donated when needed.

Preexpedition Workup

By undergoing certain procedures before the expedition, one can improve safety greatly by reducing the risk for adverse reactions and infection. These include the following:

- Screening TTDs (*e.g.*, hepatitis B and C, HIV, etc.)
- ABO typing and titrating of anti-A/anti-B antibodies in group O donors
- Field donor cards
- Vaccination according to national standard
- Proper training and awareness on when to use WFWB and its possible complications

What Do You Need — The Kit

- You need a plan! Preparedness!
- Preexpedition blood workup
- Blood collection bag with citrate-phosphate-dextrose (CPD) or citrate-phosphate-dextrose-adenine (CPDA-1) anticoagulant mixture in it
- Marker pen
- Venous restriction band

- Approved blood infusion set with filter
- ELDON cards for blood typing or similar kit
- Sterilization swabs for the puncture site
- Tape to secure the needle

Step-by-Step Procedures, according to the NORNAVSOF RDCR Protocol

Step-by-step procedures are as follows (23):

- Preexpedition workup!
- Indications to start transfusion must be met:
 - Clinical signs, combined with mechanism of injury that can cause noncompressible bleeding. Clinical signs include the following: increasing heart rate over time, altered mentation, and increasing blood lactate levels if available (consider bringing a portable lactate monitor).
- Establish an intravenous or intraosseous route. For intraosseous route, sternal access is preferred.
- The initial fluid of choice is freeze-dried plasma until WFWB is available.
- Administer 1 g of TXA.
- Patient is typed if blood type is unknown.
- Donors are screened for HIV, hepatitis C virus (HCV), and hepatitis B virus (HBV) by rapid tests (Medmira Multiplo).
- Donor and patient are matched (Fig. 2).

To make this less complicated in the austere environment, and to decrease the risk of mistakes, it is advised to prefer the use of donors with blood group O as universal donors in the first line of transfusion (22).

- While the previously mentioned steps are conducted, the donor is donating a unit of whole blood using a collecting bag containing citrate (Terumo BCT CPDA). Clear marking of the blood bag, with donor ID, date/time group, and blood type, is important to prevent ABO mismatch and transfusion of old products.
- Administer WFWB through the established route. Resuscitation end point and guidelines are difficult. Rely on clinical parameters.

Conclusions

What to do now? In the dramatic case vignette, luckily a helicopter transfer to a hospital where blood transfusion was available saved the bleeding author's life. For the next dangerous climbing activity, the lesson learned from military experience will be remembered — bring blood bags and know which hikers are potential group O donors.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Department of the Army or the U.S. Department of Defense.

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